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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KHARE, DEVESH	
ART UNIT	**PAPER NUMBER**
1623	8

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,306	WENZEL ET AL.	
	Examiner	Art Unit	
	Devesh Khare	1623	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The amendment received on 06/20/03 has been entered. The rejection of claims 1-4 under 35 U.S.C. 112, second paragraph, have been overcome through applicants' amendment to the claims.

Claims 1-12 are currently pending in this application.

Status of the Restriction (of record)

The response to restriction requirement received on 12/10/02 has been entered. Applicants' election of Group I (claims 1 and 2) with traverse in Paper No. 4 is acknowledged. In view of the similarity in the mode of action and effects of the compositions between the compositions claimed in claims 1 and 2 and a method for inhibiting COX-2 biosynthesis in claims 3 and 4 with the said composition, the restriction requirement of Group II (claims 3 and 4) is withdrawn. Applicant's arguments are convincing. Claims 5-12 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Response to Election with Traverse

Applicants further traverse the restriction requirement. The traversal is on the ground(s) that "the subject matter of claims 5-12 (Groups III and IV) relates to the same invention as of claims 1 and 2". This is not found persuasive because the applicants claims encompass three distinct classes of Groups, Group III (claims 5-7) drawn to a method of treating inflammation, rheumatoid arthritis and osteoarthritis which would be burdensome to the examiner as it cannot be assumed that the modes of a method for inhibiting COX-2 biosynthesis (Group II) would be the same for another method of Group III. Similarly, it cannot be assumed that the Group I (claims 1 and 2) drawn to

compositions selected from the flavones would be the same as drawn to a food or nutritional substance of Group IV. It is noted that examination of the three independent and distinct inventions would indeed impose an undue burden upon the examiner in charge of this application.The requirement is still deemed proper and is therefore made FINAL.

35 U.S.C. 103(a) rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nair et al. (U.S. Patent 6,194,469, filed 06-1999) in view of Yoshikumi et al. (U.S. Patent 4,440,757).

The claims 1 and 2 are directed to compositions for inhibiting COX-2(cyclooxygenase-2) or Cox-2 and NFχB(nuclear factor kappa B) biosynthesis, which comprises a bioflavonoid represented by the formula I and II where a sugar selected from glucoside, rutinoside or apiosylglucoside is attached to C-7 position in said bioflavonoid.

Nair et al. teach a composition and a method for inhibiting cyclooxygenase enzymes using a mixture of anthocyanins, bioflavonoids and phenolics (see abstract). Nair et al. disclosed the importance of plant-derived compounds as anti-inflammatory agents by inhibiting prostaglandin synthesis or cyclooxygenase (COX) enzymes (see col. 1, lines 33-35 and col. 2, lines 43-46). In column 6, lines 8-18, a composition of the mixtures of anthocyanins, bioflavonoids and phenolics is taught. In column 9, Example 5, a method to inhibit COX-2 activity by flavonoids

and isoflavonoids is disclosed (see col. 9, lines 45-60). Applicants use of formula I and II, where a glucoside is attached to C-7 position in a flavonoid for inhibiting COX-2 biosynthesis is seen to be rendered obvious, see col. 11, lines 29-34 of Nair et al., wherein the inhibitory activity of C-7 glucosylated genistin isoflavonoid is disclosed.

While the Nair et al. compositions containing the flavonoids and isoflavonoids are closely analogous to applicant's, Nair et al's. compositions differ from applicant's compositions in that the flavonoids and isoflavonoids used for inhibition studies of COX-2 are glycosylated at C-3 position, except genistin, which is glucosylated at position C-7. However Nair et al. does provide motivation to use natural products for use as cyclooxygenase inhibitors and as anti-inflammatory agents (see col. 3, lines 17-19). Use of a known member of a class of materials in a process is not patentable if other members of the class were known to be useful for that purpose, even though results are better than expected.

Yoshikumi et al. teach a pharmaceutical composition for regulating prostaglandins (see abstract). On column 6, lines 8-18, a composition for use in regulating prostaglandins is disclosed, wherein a glycosylated derivative of aminobenzoic acid represented by formula (1) is an active ingredient. Yoshikumi et al. disclose the effect of an anti-inflammatory drug, indomethacin, which relates to cyclooxygenase in the regulation of prostaglandins in col. 10, lines 65-67. It is noted that Yoshikumi et al. does not provide specific disclosures regarding the use of a bioflavonoid in the inhibition of a cyclooxygenase.

Therefore, one of ordinary skill in the art would have found the applicants claimed composition of formula I and II, to have been obvious at the time the invention was made having the above

cited references before him. Since Nair et al. teach a composition and a method for inhibiting prostaglandin synthesis or cyclooxygenase (COX) enzymes using the plant-derived compounds as anti-inflammatory agents and Yoshikumi et al. teach a pharmaceutical composition for regulating prostaglandins, one skilled in the art would have a reasonable expectation for success in combining both references to accomplish a composition comprising formula I and II and a method for regulating prostaglandin by inhibiting COX-2(cyclooxygenase-2) or Cox-2 and NFχB(nuclear factor kappa B) biosynthesis by using the said composition.

Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nair et al. (U.S. Patent 6,194,469, filed 06-1999) in view of Yoshikumi et al. (U.S. Patent 4,440,757).

The claims 3 and 4 are directed to a method for inhibiting COX-2 or NFχB or Cox-2 and NFχB biosynthesis by administering to a patient, a therapeutically effective amount of compound of claim 1 (formula I) or claim 2 (formula II).

Nair et al. teach a composition and a method for inhibiting cyclooxygenase enzymes using a mixture of anthocyanins, bioflavonoids and phenolics (see abstract). Nair et al. disclosed the importance of plant-derived compounds as anti-inflammatory agents by inhibiting prostaglandin synthesis or cyclooxygenase (COX) enzymes (see col. 1, lines 33-35 and col. 2, lines 43-46). In column 6, lines 8-18, a composition of the mixtures of anthocyanins, bioflavonoids and phenolics is taught. In column 9, Example 5, a method to inhibit COX-2 activity by flavonoids and isoflavonoids is disclosed (see col. 9, lines 45-60). Applicants use of formula I and II, where a glucoside is attached to C-7 position in a flavonoid for inhibiting COX-2 biosynthesis

according to claim 3 and 4 is seen to be rendered obvious, see col. 11, lines 29-34 of Nair et al., wherein the inhibitory activity of C-7 glucosylated genistin isoflavonoid is disclosed.
While the Nair et al's method to inhibit COX-2 activity by flavonoids and isoflavonoids are closely analogous to applicant's, Nair et al's. compositions differ from applicant's compositions used in the said method in that the most of flavonoids and isoflavonoids used for inhibition studies of COX-2 are glycosylated at C-3 position, except genistin, which is glucosylated at position C-7. However Nair et al. does provide motivation to use natural products for use as cyclooxygenase inhibitors and as anti-inflammatory agents (see col. 3, lines 17-19).

Yoshikumi et al. teach a pharmaceutical composition for regulating prostaglandins (see abstract). On column 6, lines 8-18, a composition for use in regulating prostaglandins is disclosed, wherein a glycosylated derivative of aminobenzoic acid represented by formula (1) is an active ingredient. Yoshikumi et al. disclose the effect of an anti-inflammatory drug, indomethacin, which relates to cyclooxygenase in the regulation of prostaglandins in col. 10, lines 65-67. It is noted that Yoshikumi et al. does not provide specific disclosures regarding the use of a bioflavonoid in the inhibition of a cyclooxygenase.
Therefore, one of ordinary skill in the art would have found the applicants claimed method for inhibiting COX-2 biosynthesis with a composition containing formula I and II, to have been obvious at the time the invention was made having the above cited references before him. Since Nair et al. teach a composition and a method for inhibiting prostaglandin synthesis or cyclooxygenase (COX) enzymes using the plant-derived compounds as anti-inflammatory agents and Yoshikumi et al. teach a pharmaceutical composition for regulating prostaglandins, one

skilled in the art would have a reasonable expectation for success in combining both references to accomplish a composition comprising formula I and II for a method for regulating prostaglandin by inhibiting COX-2(cyclooxygenase-2) or Cox-2 and NFχB (nuclear factor kappa B) biosynthesis.

Rejection Maintained

Rejection of claims 1-4 under 35 U.S.C. 103(a) is maintained for the reasons of record.

Response to Arguments

Applicant's arguments filed on 06/20/03 traversing the rejection of claims 1-4 under 35 U.S.C 103(a) have been fully considered but they are not persuasive.

Applicants argue that "the examiner does not discriminate between the inhibition of an enzyme and the inhibition of the biosynthesis of the enzyme". It is noted that according to Nair et al., COX-1 and COX-2 enzymes are involved in prostaglandin synthesis (col. 2, lines 51-53). Furthermore, Nair et al. disclose that the flavonoids are now being investigated as anti-inflammatory substances as well as their structural features for cyclooxygenase (COX) activity (col. 2, lines 59-61).

Applicants argue that "Yoshikumi et al. merely teach pharmaceutical compounds for regulation of protaglandins which have no structural feature in common with the compounds disclosed in the present application". It is noted that applicant's compounds of formula I and II are flavonoid wherein the phenyl ring is substituted at C-7 position by a glucoside group. Yoshikumi et al. disclose a series of derivatives of aminobenzoic acid wherein the phenyl ring is substituted with glucose, which are active in regulating prostaglandin synthesis without exhibiting side effects (col. 1, lines 30-42 and 65-67).

2. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Devesh Khare whose telephone number is (703)605-1199. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Supervisory Patent Examiner, Art Unit 1623 can be reached at 703-308-4624. The official fax phone numbers for the organization where this application or proceeding is assigned is (703) 308-4556 or 308-4242.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Devesh Khare, Ph.D.,JD(3Y).
Art Unit 1623
October 17,2003